Solubility Enhancement Methods - A Promising Technology for Poorly Water Soluble Drugs

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ABSTRACT
The most challenging task in drug development is enhancement of solubility, dissolution rate, and bioavailability of drug. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Drug to be absorbed should be in solution form at the site of absorption. Absorption of orally administered drugs will take place only when they show fair solubility in gastric medium and such drugs show good bioavailability. Solubility and dissolution properties of drugs play an important role in the process of formulation and development. Major challenge for formulation scientist is the solubility problem which can be solved by different technological approaches during the pharmaceutical product development work. This review gives detailed information about various technologies used for enhancing solubility and dissolution of poorly soluble drugs, including nanotechnology methods for enhancing solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development. Selection of this solubility enhancing method mainly depends on drug property, site of absorption and dosage form characteristics.

Keywords: Solubility, Enhancements techniques, Novel methods, Bioavailability, Lipid technology.

INTRODUCTION
About 10% of new chemical entities lack there launching in market due to their poor water solubility and in spite of their potential pharmacokinetic activity and 40% of new chemical entities currently discovered are poorly water soluble, and currently 8% of new drug candidates have both high solubility and permeability. The knowledge of solubility and permeability of the active ingredients led the way to the BCS (Biopharmaceutics classification system) given by Dr.Gordon Amidon, consisting of four classes of drugs. In the process of formulation development, solubility and dissolution properties of drugs play an important role. Drugs which are poorly soluble leads to poor dissolution in the gastro intestinal tract and hence incomplete and erratic absorption which limits the clinical utility. More over these drugs are administered at high doses than the actual doses to achieve drug plasma levels leading to adverse reaction, erratic pharmacological response and less patient compliance. Solubility can be defined as the ability of one substance to form a solution with another substance. The substance dissolved is called solute and dissolving fluid in which the solute dissolve is called solvent, which together form solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water. Solubility problem which can be solved during product development by choosing some technological approaches and Solid dispersion, Micronization, Salt formation are some approaches usually used to enhance solubility but each approach has limitations and advantages. Now novel technologies like Nano suspension, Supercritical processing, Crogenic technology has opportunities in the delivery of poorly soluble drugs.

Importance of solubility
Solubility is an important parameter in case of oral administered drugs in order to achieve desired concentration of drugs in the systemic circulation to show the pharmacologic response. Oral route is the most preferred route because of its ease of administration, cost effectiveness, patient compliance and sterility constraints are least needed, and most of the generic drug companies are interested more to produce bioequivalent oral drug products. And major challenge in the design of oral dosage form is its poor bioavailability. The oral bioavailability mainly depends on some factors like aqueous solubility, drug permeability, dissolution rate; first pass metabolism etc and the most usual cause of low oral bioavailability are because of poor solubility and low permeability. In the case of parental formulation also solubility plays an important role. This review article describes about the various techniques used to enhance the solubility of poorly soluble drugs, and these techniques are chosen based on some properties of drugs under consideration, excipients nature and nature of dosage form.

SOLUBILITY ENHANCEMENT TECHNIQUES
Solubility of poorly soluble drugs can be improved by using various techniques. Some of the techniques are:

Physical Modifications
1. Particle Size Reduction

Micronization: The solubility of drug is often related to the particle size of drug. Decrease in the particle size will lead to increase in the surface area and thereby dissolution can be increased, and micronization is a...
process by which dissolution can be increased through increased surface area but it does not increase the equilibrium solubility. Micronization is done using jet mill, rotor stator colloid mills etc.

Nanosuspension: Sub-micron colloidal dispersion of pure particles of drugs which are stabilized by using surfactants is called Nanosuspensions. The most important advantage of nanosuspension is the increased dissolution rate due to increase in the surface area. Homogenization and wet milling are some techniques used for the production of nanosuspensions. Nanosuspensions can be dried by using lyophilisation or spray drying techniques.

Sonocrystallisation: By using ultrasound particle size reduction can be done on the basis of crystallisation and this is a novel approach and in this method ultrasound power characterised by a frequency range of 20-100 kHz are used for inducing crystallisation. 

Supercritical fluid process (SCF): A super critical fluid (SF) can be defined as a dense non condensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). Micronisation of drug particles, often to sub micron levels can be done by SCF. Rapid expansion of supercritical solutions and gas antisolvent recrystallisation are the most widely used method of SCF processing for micronized particles, and carbon dioxide is used as SCF due to its properties like low critical temperature and pressure.

### Table 1: Supercritical fluid along with their properties

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Molecular Weight (g/mol)</th>
<th>Critical Temperature (k)</th>
<th>Critical Pressure [MPa (atm)]</th>
<th>Density (g/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon dioxide</td>
<td>44.01</td>
<td>304.1</td>
<td>7.38(72.8)</td>
<td>0.469</td>
</tr>
<tr>
<td>Water</td>
<td>18.02</td>
<td>647.3</td>
<td>22.12(218.3)</td>
<td>0.348</td>
</tr>
<tr>
<td>Methane</td>
<td>16.04</td>
<td>190.4</td>
<td>4.60(45.4)</td>
<td>0.162</td>
</tr>
<tr>
<td>Ethane</td>
<td>30.07</td>
<td>305.3</td>
<td>4.87(48.1)</td>
<td>0.203</td>
</tr>
<tr>
<td>Propane</td>
<td>44.09</td>
<td>369.8</td>
<td>4.25(41.9)</td>
<td>0.217</td>
</tr>
<tr>
<td>Ethylene</td>
<td>28.05</td>
<td>282.4</td>
<td>5.04(49.7)</td>
<td>0.215</td>
</tr>
<tr>
<td>Propylene</td>
<td>42.08</td>
<td>364.9</td>
<td>4.60(45.4)</td>
<td>0.232</td>
</tr>
<tr>
<td>Methanol</td>
<td>32.04</td>
<td>512.6</td>
<td>8.09(79.8)</td>
<td>0.272</td>
</tr>
</tbody>
</table>

2. **Modification Of The Crystal Habit**

Polymorphic modification of drug: Ability of a compound to crystallize in more than one crystalline form is called polymorphism. Polymorphic forms of the drugs are chemically identical, but they show difference in the properties like solubility, melting point, density, texture, and stability. Based on the thermodynamic properties polymorphs can be classified into enantiotropes and monotropes. Similarly drug which is in amorphous form is more suited than crystalline form due to higher energy and increase in surface area and when compare to hydrates, the anhydrous form of drug have high solubility.

3. **Drug Dispersion In Carriers**

Solid dispersion: Dissolution rate, solubility and oral absorption of poorly soluble drugs can be improved by technique called solid dispersions (figure 2).
This method is mainly used to reduce the particle size, there by dissolution and absorption of drugs can be increased. Dispersion of one or more active ingredients in an inert carrier in solid state is called solid dispersions and usually prepared by melting method, fusion method or fusion solvent method. For solid dispersions the commonly used hydrophilic carriers are polyvinylpyrrolidone,\textsuperscript{12} and plasdone-S630.\textsuperscript{13} Surfactants can also be used in the preparations of solid dispersions. eg- Tween80, Myrij-52, pluronic-F68. By using suitable hydrophilic carriers the solubility of itraconazol,\textsuperscript{14} celecoxib\textsuperscript{15} can be improved by solid dispersion.

Solid Solutions: This is a binary system consisting of a solid solute molecularly dispersed in a solid solvent. The two compartments crystalize together in a homogenous one phase system; solid solutions are also called as molecular dispersion. By this method particle size can be reduced resulting in greater aqueous solubility and dissolution. Solid solutions are prepared by fusion method.\textsuperscript{16}

4. Complexation

Use of complexing agents: Complexation is method of association between two or more molecules to form a nonbonded entity with a well defined stiochiometry. When compare to all methods of solubility enhancement, inclusion complex formation technique is the widely used method to improve the solubility, dissolution rate and bioavailability of poorly soluble drugs. Complexation with cyclodextrins is most commonly used because it has the property to alter the physical, chemical and biological properties of guest molecules by the formation of inclusion complexes. Cyclodextrins are non reducing, crystalline, water soluble, and oligosaccharides consisting of glucose monomers arranged in donut shaped ring having hydrophilic cavity and outer hydrophilic surface. Cyclodextrins are of three type's alpha, beta and gamma cyclodextrins. Various technologies have been adapted to complex the poorly soluble drug with cyclodextrins. Some methods are kneading method, co-precipitation method, and solvent evaporation method, co-grinding method, lyophilisation, and spray drying method.\textsuperscript{17}

Solubilisation by using surfactants: Surfactants are molecules with distinct polar and non Polar Regions. Surfactants mainly consist of hydrocarbon segment connected to a polar group. The polar group may be anionic, cationic, or zwitterions or non ionic like polyethylene glycol, glycerol. Surface tension can be reduced with help of surfactants there by dissolution of lipophilic drugs can be improved. When the concentration of surfactant exceeds their critical micelle concentration, micelle formation occurs which entrap the drug within the micelles and the process is called micellization and which result in the enhanced solubility of poorly soluble drugs.\textsuperscript{5,18}

Micro emulsions: A micro emulsion is a four component system which composed of external phase, internal phase, surfactant and co-surfactant. The addition of surfactant, which is soluble in internal phase, results in the formation of an optically, clear, isotropic, thermodynamically stable emulsion. When compare to coarse emulsions, formation of micro emulsion is spontaneous and does not involve the input of external energy, and micro emulsions have advantages over coarse emulsions.\textsuperscript{18,19}

- Ease of preparation due to spontaneous formation.
- Thermodynamic stability.
- Transparent and elegant appearance.
- Drug loading can be increased.
- Increased bioavailability.
- Less intra and inter-individual variability in drug pharmacokinetics.
- Penetration through biological membrane is high.

Chemical Modification

1. By using salt form

The most common method used to increase the solubility is by using salt form, this method mainly used to increase the dissolution of acidic and basic drugs. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drug like atropine are more water soluble than the parent drug.\textsuperscript{18}

Limitations of salt form:

- Poor processing characters, sometimes exhibit polymorphism and are hygroscopic in nature.
- Difficult to form salt of weak bases or acids.
- Difficult to form salts of neutral compounds.

2. By changing the pH

Organic solutes which are ionisable in nature, changing the PH of the system are most suitable way to increase the solubility. By adjusting the ph of the solution under proper condition, the solubility of ionisable drugs can be increased exponentially but the drug should be either weak acid with a low pka or a weak base with a high pka.\textsuperscript{16}

Other methods of solubility enhancement

1. Co-crystallisation

Enhancement of drug solubility can be done by using a new technique by using co-crystals. A co-crystal may be defined as a crystalline material that consists of two or more molecular species that held together by non - covalent forces. Co-crystals are stable and solids at room temperature. These agents are generally considered safe, but only three co-crystallizing agents are generally recognized as safe eg-saccharin, nicotinamide and acetic acid.\textsuperscript{1} Co-crystals are prepared by grinding the components together or by evaporation of a heteromeric solution. Other methods are slurry preparation;
sublimation. This method can be considered an alternative for salt formation mainly in the case of neutral compounds.

2. Co-solvency

By using co-solvents the solubility of poorly soluble drugs can be improved, and addition of an organic solvent to water can dramatically change the solubility of drugs. But altering the polarity of the solvent, the water solubility of weak electrolytes and non polar molecules can be improved, this can be obtained by the addition of another solvent. This is called co-solvency. This system can reduce the interfacial tension between the aqueous solution and hydrophobic solute. By using 20% of 2-pyrrolidone solubility can be enhanced as high as 500 fold.

3. Solubilising agents

Various solubilising materials are used improve the solubility of poorly water soluble drugs. PEG400 is used to improve the solubility of hydrochlorothiazide. A recently developed excipient called modified gum karaya was used as a carrier for enhancing the dissolution of poorly soluble drugs, nimodipine.

4. Hydrotrophy

This is one of the solubilisation techniques, whereby the addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Hydrotropes are compounds containing an anionic group and hydrophobic aromatic ring, and anionic group help to increase the hydrophilicity and the ring system interacts with the solute to be dissolved. When hydrotropes are added to aqueous surfactant or polymer solutions, often synergistic effects are observed. (Table 2)

Table 2: Agents used for hydrotropic solubilisation of drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Additive used to exhibit hydrotropism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefadroxil</td>
<td>Potassium acetate, potassium citrate</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Sodium acetate, Urea</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Sodium salicylate</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Sodium salicylate</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Urea, sodium citrate</td>
</tr>
</tbody>
</table>

5. Hot Melt Extrusion Technique

Extrusion can be defined as the process of forming a new material by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed rate, and pressure. By this technique the absorption and dissolution properties of poorly soluble drugs can be improved.

6. Solvent Deposition

Nifedipine, poorly aqueous soluble drug is dissolved in an organic solvent like alcohol, and deposited on an inert, hydrophilic solid matrix such as starch by evaporation of solvent.

7. Selective adsorption on insoluble Carrier

Inorganic clays like bentonite which is highly active adsorbant can enhance the dissolution of poorly soluble drugs such as griseofulvin, indometacin, by maintaining concentration gradient at its maximum. The weak physical bonding between adsorbent and adsorbate may be the reason suggested for the rapid release of drugs from the surface of the clay or hydration and swelling of the clay in the aqueous media.

8. Clathrates

A type of inclusion compound in which the host molecules form a crystal lattice containing spaces into which guest molecules can fit. The macro cyclic molecule is called the guest, this give rise to host-guest chemistry. The host molecule must be hydrophilic in nature and able to bind the lipophilic guest molecule by hydrophobic interactions.

Nanotechnology Approaches

This technology is mainly used to improve the solubility of poorly soluble drugs. Nanotechnology refers to the study and use of materials and structures at the nano scale level ie, about 100nm (nanometre) or less. Low solubility drugs there bioavailability can be improved by using micronization, but this have disadvantage that micronized product has tendency of agglomeration which result in decrease in surface area for dissolution and the next step taken was Nanonisation.

1. Nanocrystal

Crystalline material which having dimensions in nanometer is called nanocrystal usually size range of 1-1000nm. Nanocrystallization is a universal method and can be applied to any drug. two methods are used for producing nanocrystals, bottom-up (Precipitation and Cryo-vacuum method) and top-down method (Milling and High pressure homogenization). Some of the marketed product formulated by this technology given in (Table 3).

Table 3: Current marketed product based on nanocrystal technology

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPAMUNE®</td>
<td>Sirolimus</td>
<td>Wyeth</td>
</tr>
<tr>
<td>PAXCEED</td>
<td>Paclitaxel</td>
<td>Angiotech</td>
</tr>
<tr>
<td>TRIGLIDE™</td>
<td>Fenofibrate</td>
<td>First Horizon Pharmaceutical</td>
</tr>
<tr>
<td>TRICOR®</td>
<td>Fenofibrate</td>
<td>Abbott</td>
</tr>
<tr>
<td>EMEND®</td>
<td>Aprepitant</td>
<td>Merck</td>
</tr>
<tr>
<td>AVINZA®</td>
<td>Morphine Sulphate</td>
<td>King Pharmaceutical</td>
</tr>
</tbody>
</table>
Approaches for making nanocrystals:

Milling: By the process of wet milling nanoscale particles can be produced, in ball mills particle size reduction is achieved by impact and attrition forces. Disadvantage of this method is the degradation of mill surfaces and subsequent contamination of suspension.

1. High pressure homogenization

Homogenization can be performed in water (Disso cubes) or in non-aqueous media or water reduced media (nanopure). In high pressure homogenization, an aqueous dispersion of the crystalline particles is passed through a narrow homogenization gap with a very high velocity. A heat exchanger should be used when using temperature sensitive materials because high pressure homogenization may cause increase in sample temperature.28,33

2. NanoMorph Technology

This technique is to convert drug substance with low water solubility from coarse crystalline into amorphous nanoparticles. Under this technology crystalline drug substance are transformed into nanodispered amorphous state without any physical milling or grinding procedures. It leads to the preparation of amorphous nano particles.34

3. Dissocubes

This technology is based on piston-gap high-pressure homogenization. Advantage of this technology is1
- Ease of scale up.
- Little batch-to-batch variation.
- Aseptic production for parenteral administration.

4. Nanoedge technology

This technology is mainly used for poorly soluble drugs, mainly used for active ingredients that have high melting point and high octanol-water partition coefficients.1

5. Nanopure technology

In this technique, poorly water soluble drugs are transferred to drug nano crystals by high pressure homogenization process. The powder form of drug is dispersed in a surfactant solution and the forces in the high pressure homogenizer are sufficient enough to disintegrate the coarse powder into drug nanoparticles i.e., 200-600nm.35

6. Cryogenic technology

By this novel technology, particles with greater surface area can be produced, thereby increasing the dissolution rate of drugs by creating nanostructured amorphous drug particles with high porosity at very low temperature. After cryogenic processing, dry powder can be obtained by various drying processes like spray drying, vacuum freeze drying, atmospheric freeze drying, and lyophilisation.36,37

7. Cryo-vacuum method

In this method active ingredient to be nano sized. First dissolved in water to attain quasi saturated solutions. The method is based on sudden cooling of a solvent by immersing the solution of liquid nitrogen. Rapid cooling causes a very fast rise in the degree of saturation based on the decrease of solubility and development of ice crystals when the temperature drops below 0°C. This leads to fast nucleation of the dissolved substances at the edges of the ice crystals. The solvent must be completely frozen before the vessel is removed from the liquid nitrogen. The next solvent is removed by sublimation in a lyophilisation chamber where the temperature is kept at constant-22°C and the pressure is lowered to 10^{-7} mbar. Cryo- assisted sublimation makes it possible to remove the solvent without changing size and habit of particles produced, so they will remain crystalline. This method yields very poor nano crystals since there is no need to use surfactants or harmful reagents.18

8. Crititech technology

This technology uses ultra sonic energy produced by a converging-diverging nozzle or an electromechanical oscillator to shatter droplets into even droplets. This technique alone would not cause submicron particles to form because the droplets tend to coalesce immediately into larger droplets. The procedure is the drug-laden solvent is sprayed into a flowing stream of super critical carbon dioxide, which allows a rapid mass transfer of solvent into a stream of super critical carbon dioxide. This rapid mass transfer forces precipitation or crystallization to occur before the coalescence of droplets. The ultra sonic nozzle based process is capable of producing nano particles in a narrow size range.1

9. Nanocochleate technology

Also known as bioral technology used for the delivery of many therapeutic products. This is mainly composed of molecules which are stable phosphor lipid cation precipitates composed of simple naturally occurring materials such as phosphatidylserine and calcium. This nanocochleates have been used to enhance oral bioavailability of a broad spectrum of important but difficult to formulate biopharmaceuticals, including compounds with poor water solubility, protein and peptide drugs. This technology is used for the oral delivery of amphotericin B (bioral amphotericin B), peptide formulations, and anti-inflammatory formulations (bioral aspirin).1,38

Lipid Technology

Lipid technology is the most prominent and latest method for increasing the solubility of poorly water soluble drugs. Fine dispersion of poorly water soluble drugs can be produced by lipid formulations. Slow and incomplete dissolution of poorly soluble drugs can be reduced by lipid technology. Various lipid systems are explained here.
Oil based formulations

Oil based formulations offer many advantages in the formulating poorly water soluble drugs. For oral delivery oils may be used as vehicles. Lipids are ideally prepared as unit dosage form such as sealed hard or soft gelatine capsules. Soft gelatine capsules are generally accepted by the consumers because it is easy to swallow and its elegance. But this type of formulations is not widely employed due to interaction of the fill with the soft gelatin shell, limited solubility of some drugs in the lipid solvents need to incorporate suspending agent for poorly water soluble drugs. Eg. Halofantrine hydrochloride is a new important ant malarial water insoluble drug. There was a 3-fold increase in the mean oral bioavailability of 250 mg Halofantrine hydrochloride when administered with a fatty meal to human subjects. 39

Lipid emulsions

Emulsions are heterogeneous systems in which one immiscible liquid is dispersed as droplets in another liquid, this is suitable for both passive and active drug targeting. Better tolerated intravenous formulations of poorly water soluble drugs prepared by lipid emulsion drug delivery system. Micro emulsions are iso tropic and thermo dynamic stable multi component fluids composed of water, oil, surfactant and co-surfactant. In micro emulsions droplet size range from 100 A to 1000 A. Multiple emulsions are complex system and they are called emulsions of emulsions, double or triple emulsions because of the internal phase containing dispersed globules which are miscible with the continuous phase. These systems are characterized by their low thermodynamic stability. 40

Emulsome

This system have wide range of therapeutic applications especially for parenteral delivery of drugs which are poorly water soluble. These systems are often prepared by melt expression or emulsion solvent diffusive extraction. 41

Solid lipid nano particles

These systems are sub micron colloidal carriers which are composed generally of lipid dispersed in water or in an aqueous surfactant solutions. Site specific drug delivery can be achieved because of its small size and relatively narrow size distribution. Controlled and sustained release of active drug can be achieved and this is relatively cheap and stable and can be lyophilized and incorporated drug can be protected from biochemical degradation. Micro emulsion technique can be used for the preparation of solid lipid nano particles. The hot micro emulsion containing the lipid poured into the cold water leading to solidification of nano particles and this possess lower cytotoxicity. 42, 43

Self Emulsifying Drug Delivery System (SEDDS) and Self Micro Emulsifying Drug Delivery System (SMEDDS)

Mixture of lipid excipients and surfactants to produce self emulsifying drug delivery systems 44, 45 and micro emulsifying drug delivery system for oral administration of poorly water soluble drugs. These are formulations that form emulsions or micro emulsions spontaneously on contact with aqueous media. SMEDDS generally contain high concentration of surfactant and hydrophilic co-solvents. This technology is used for the oral administration of cyclosporine (Neoral-Novartis). The bioavailability of ontazolast was significantly enhanced by lipid based formulations. 46

CONCLUSION

The basic approaches followed in all the currently used method for solubility enhancement and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, better patient compliance and low cost of production. Older methods of solubility enhancement had a problem of irregular shape or size; larger particle size which leads to irregular dissolution, but novel method shown the properties of uniform size which can be used in combination or alone will have potential for the dissolution enhancement of the newer chemical entities. Lipid technology is the latest trend which has affected the Pharma field and is growing by leaps and bounds. Many methods have been patented and future belongs to lipid technology. Dissolution enhancement of poorly water soluble drugs constitute innovative approach which overcome the problem of solubility of dissolution rate limiting step and provide a quick own set of action.

REFERENCES

3. Indian Pharmacopoeia, Ministry of Health and family welfare, Government of India, Published by the controller of publications, Delhi, 1,1996, 1-7.
7. Blagden N, De Matas M , Gavan PT; Crystal engineering of active pharmaceuticals ingredients to improve solubility.


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